

Exhibit 3

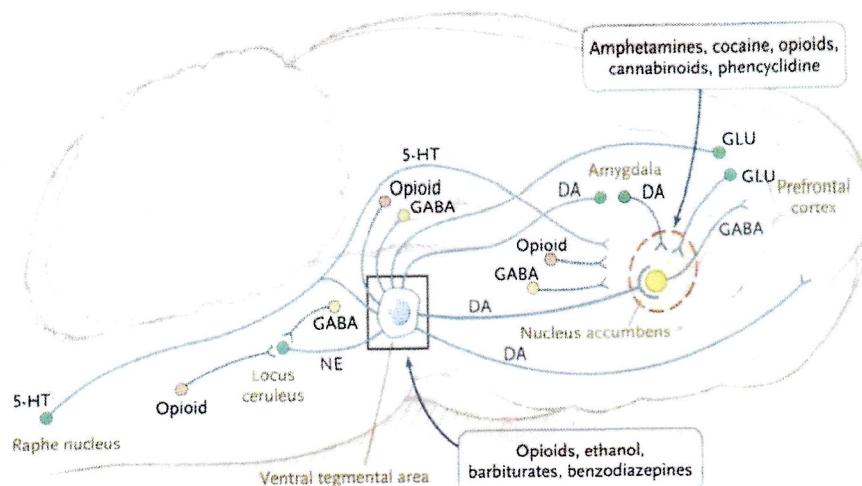


FIGURE 59.1 Common reward pathway: mesocorticolimbic dopamine (DA) system. (Reproduced from Cami J, Farre M. Drug addiction. *N Engl J Med* 2003; 349(10):975-986, with permission.)

nized increases in tumor burden.²² Pharmacodynamic tolerance involves adaptations that occur at both the site of the drug action (e.g., receptor and ion channel), as well as in related systems more distal to it. For example, pharmacodynamic tolerance to opioids is evident at both the level of the opioid receptor in the locus ceruleus (primary) and in the dopaminergic reward pathways afferent to the site of this discrete drug action (secondary).¹⁹ Both persons addicted to heroin and chronic pain patients taking opioids can exhibit tolerance to the drug.

Binary Concept of Pain and Addiction

In the past, the literature has suggested that pain conditions and addictive disorders might be dichotomous phenomena.^{5,7,23} It has been said that in the context of a "legitimate" pain diagnosis, which usually meant a condition that made sense to the assessing health care professional, the likelihood of there being an addictive disorder was so small as to not even merit investigation. Unfortunately, if the patient had an obvious substance use disorder, very real and treatable pain conditions were often ignored. With time, this thinking was tempered somewhat to suggest that in the absence of a current or past personal or family history of a substance use disorder, the risk of addiction was very low indeed.⁵ This dichotomous approach to pain and addiction has not served patients, health care professionals, or society well.

In reality, there is nothing about a genuine pain condition that is protective against having a concurrent substance use disorder; however, untreated pain, as a stressor, should be considered in the assessment of relapse risk.¹⁵ While there are some data in the animal literature to suggest that acute pain may blunt the euphoric reward of some drugs including opioids,^{24,25} the ability to generalize this phenomenon to the human population and more importantly, the sustainability of this "protection" has yet to be established. Patients with a substance use disorder are often disproportionate consumers of health care resources, especially in the context of trauma.^{26,27} The presence of a preexisting substance use disorder is not mitigated by a concurrent pain problem; it is complicated by it.

While there is no evidence in the literature to suggest that those patients without past histories or increased risk of substance use disorders become addicted as a result of rational pharmacotherapy for the treatment of any medical condition, including chronic pain, there is little credible evidence to the contrary either. Perhaps more relevant questions to ask are whether rational phar-

macotherapeutic management of acute or chronic pain can reactivate a previously dormant substance use disorder or express an as yet unidentified genetic predisposition toward substance misuse or addiction. In the authors' opinion, the answer to both questions is very likely, "Yes."⁷

Risk, of course, varies with circumstance. For example, the prevalence of alcoholism in the hospitalized general medical population is estimated at 19% to 26%,²⁸ while in the trauma subset, the prevalence rises to 40% to 62%.²⁷ Regardless of what the actual risk is, it is clear that no one specific marker can reliably identify the at-risk pain patient, so careful boundary setting for all patients is strongly recommended.⁵

Not all aberrant behavior reflects drug misuse or addiction. Some individuals who do not meet the diagnostic criteria for addiction may also use medications and other drugs problematically. This group is sometimes referred to as "chemical copers."²⁹ These individuals lack the skills commonly acquired during childhood and adolescence and tend to turn to external sources for support in dealing with life's problems. More often than not, however, these patients suffer from complex, multidimensional problems that may only be partially responsive to even optimum pharmacotherapy in the absence of a biopsychosocial treatment plan. Unidimensional problems may respond to unidimensional pharmacologic solutions. Multidimensional problems, however, may transiently respond to pharmacologic interventions, but rarely in a sustainable fashion.⁷

It is only by aggressive investigation and rational pharmacotherapeutic management of the pain that this diagnosis can be made. The diagnosis of addiction is often made prospectively, over time. When the patient's behavior remains aberrant despite the appropriate management of the underlying painful condition with reasonably set limits, substance misuse or addiction should be considered. In contrast, the diagnosis of pseudoaddiction is made retrospectively in that with appropriate management of pain, aberrant behavior is reduced or eliminated.^{5,7} When reasonable limits and boundaries are placed on a patient and yet the patient continues to step out beyond these limits, addiction and pseudoaddiction should be in the differential diagnosis.

Boundary setting may include interval dispensing and contingency prescribing. Interval dispensing requires the patient to see other members of the health care team, such as a staff member, of the prescriber or the pharmacist on a more frequent basis than the actual prescriber. Thus, interval dispensing can be a simple and effective means to help patients keep from "borrowing from tomorrow to pay for today," thereby reducing the risk of running

out of medications early. With contingency prescribing, receiving the next prescription is contingent on something such as bringing bottles in for "pill counts" or mandatory attendance at all appointments.

Pain and Opioid Addiction—A Continuum Approach

While pain and addiction can and sometimes do exist as comorbid conditions, they may also be present as part of a dynamic continuum with pain at one end of the spectrum and addiction at the other (Fig. 59.2).^{7,23} In cases where the identified substance of misuse is one in which there can be no doubt about the medical appropriateness of its use, such as with alcohol or cocaine, a comorbid pain and substance use disorder should be considered. However, when the drug in question can arguably be both the problem and the solution, depending on the health care professionals' training and perspective, a continuum model may better apply.^{7,23} With chronic pain, appropriateness of ongoing opioid use should be periodically evaluated, especially when there is little or no objective evidence of improvement in pain relief or function.

In cases in which pain and addiction coexist either as a continuum or comorbid condition, it is important to identify which aspect of the illness is dominant. Failure to treat both conditions, when present, will undoubtedly lead to frustration and poor outcomes in both domains. It is equally important to realize that this continuum is dynamic, with substance use disorder symptoms becoming dominant during periods of stress even after years of stable recovery.^{7,23}

Separating the "Motive" from "Behavior" when Dealing with Pain and Addiction

One of the greatest challenges facing practitioners treating complex pain patients is dealing with the patient who explains his or her aberrant behavior in terms of his or her chronic pain. Not infrequently, the health care professional will hear the patient say, "But I'm not an addict, I'm a pain patient" when challenged with explaining why he has run out of medication early, yet again. Of course, interpreting such behavior can be challenging.³⁰ The differential diagnosis is long and includes dependence, pseudo-addiction, true addiction, comorbid psychopathology, "chemical coping,"²⁹ and even criminal behavior such as diversion.⁷ More often than not, the patient and/or patient's family can identify and are willing to discuss the aberrant behavior in the context of a "problem," rather than as evidence of a possible substance use disorder.

Take for example the patient who has unilaterally escalated his or her daily dose of medication, necessitating an early return

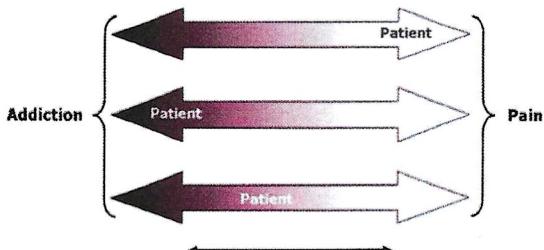


FIGURE 59.2 Pain and addiction continuum. (Adapted from Heit HA, Gourlay D. Chronic pain and addiction. In: Pasricha PJ, Willis WD, Gebhart GF, eds. *Chronic Abdominal and Visceral Pain: Theory and Practice*. New York: Taylor and Francis, 2006:231–244, with permission.)

for prescription renewal. While this may occur occasionally for quite legitimate reasons, repeated unilateral dose increases reflect behavior that must be carefully evaluated. In such a case, it may be more useful to focus on the problematic behavior (running out early) rather than the motive behind the behavior (i.e., addiction/abuse, chemical coping, etc.) when exploring this with the patient. Once the problematic behavior is identified and a remedial course of action selected, the ease with which the patient adheres to this "solution" will help to identify which aspect of the aberrant behavior differential is likely at work. Patients whose problematic behavior remains unchanged despite conservative efforts likely suffer from more complex problems that would best be referred to a substance-use-disorder professional or other clinician with greater experience and resources to assess and manage these more challenging cases. Non-forensic, patient-centered urine drug testing (UDT), which is discussed in Chapter 60, can be a very useful tool in these cases.^{5,31,32}

In the case of criminal behavior, such as diversion of the prescribed medications, the behavior and motive behind it are clearly unacceptable. In the authors' opinion, this is cause to sever the doctor-patient relationship and dismiss the patient from the practice. Dismissing patients for such criminal behavior is unlikely to be construed as abandonment in most jurisdictions.

Opioids for Analgesia or Opioid-Stabilizing Effect?

Not all pain syndromes are equally responsive to opioids.³³ Neuropathic pain may be less opioid responsive, often requiring higher doses.³⁴ In cases in which a patient is physically dependent on opioids, as one would expect with prolonged use of this class of drug, it can sometimes be useful to consider the appropriateness of continuation of opioid therapy, especially when treatment goals of improved function and decreased pain remain unmet.

Most pain is, to some degree, opioid responsive. Yet, despite years of experience with opioid therapy, it remains unclear who in advance will achieve a sustained response.

When the patient and clinician define the need to remain on opioid therapy not by how well the patient is doing but rather by how poorly things go when they try to reduce or discontinue the drug, it is time to reexamine the therapeutic role of opioids. When opioid levels in a physically dependent pain patient become inadequate, early withdrawal may occur. In the context of opioid-abstinence-induced hyperalgesia, it would be expected that the pain complaint might worsen.¹³ It is something of a myth that patients who no longer need opioids always come off them easily. In any trial of therapy, including opioid pharmacotherapy, there must be a clear exit strategy in addition to an entrance, stabilization, and maintenance strategy before writing the first prescription.^{7,35} This is not to say that those patients who are clearly benefiting from opioid pharmacotherapy should be weaned from these medications on the assumption that they "may no longer need them," but rather that not all persons who have inadequate pain relief or function while on opioids should remain on this class of drugs. In fact, some persons with poorly controlled pain while on opioid therapy may improve with a carefully executed opioid taper. The term taper is used here rather than detoxification, which is a term more commonly associated with the disease of addiction. Pain patients are "tapered," and addiction patients are "detoxed." In some jurisdictions, this can be a critical distinction in medicolegal terminology.

Recommendations for Terminating Opioid Therapy

A trial of opioid therapy is just that: a trial. In some cases, a decision to discontinue opioids is made. While the optimum case is one in which both the clinician and the patient feel this is the appropriate course to take, not infrequently it is the clinician